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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/018,373	12/06/2001	Hans Bigalke	Merz 32 PCT US/dln	4496

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THE FIRM OF HUESCHEN AND SAGE
500 COLUMBIA PLAZA
350 EAST MICHIGAN AVENUE
KALAMAZOO, MI 49007

EXAMINER	
FORD, VANESSA L	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 07/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/018,373	BIGALKE ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This Office Action is responsive to Applicant's amendment and response filed April 2, 2004. Claim 11 has been amended. Claims 1-10 have been cancelled.

2. The text of those sections of the Title 35, U.S. code not included in this action can be found in the prior Office Action.

Rejections Withdrawn

3. In view of Applicant's amendment the following rejections are withdrawn.

a) objection to the specification, page 2, paragraph 2.

b) objection to the claims 7 and 10, page 2, paragraph 3.

c) rejection of claims 7-10 under 35 U.S.C. 101, page 3, paragraph 4.

d) rejection of claims 7-10 under 35 U.S.C. 112, second paragraph, page 3, paragraph 5.

e) rejection of claim 10 under 35 U.S.C. 112, second paragraph, page 3, paragraph 6.

f) rejection of claim 11 under 35 U.S.C. 112, second paragraph, page 4, paragraph 7.

g) rejection of claim 11 under 35 U.S.C. 112, second paragraph, page 4, paragraph 8.

h) Rejection of claims 7, 10 and 16-18 under 35 U.S.C. 102(b), pages 6-7, paragraph 10.

i) Rejection of claims 8-9 under 35 U.S.C. 102(b), pages 6-7, paragraph 10.

j) Rejection of claims 8-9 under 35 U.S.C. 102(b), page 7, paragraph 11.

k) Rejection of claims 7-13 and 16-18 under 35 U.S.C. 103(a), pages 8-10, paragraph 12.

l) Rejection of claims 7-12 and 14-18 under 35 U.S.C. 103(a), pages 10-12, paragraph 13.

New Grounds of Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 11-12 are rejected under 35 U.S.C. 103(a) as unpatentable over Goeschel et al, *(Experimental Neurology, 147, 1997, pages 96-102)* in view of Borodic et al *(Ophthalmic Plastic and Reconstructive Surgery, Vol. 9, No. 3, p. 182-190)*.

Claims 11-12 are drawn to method of treating a human or animal with a cosmetic condition treatable with a botulinum neurotoxin comprising administration to the human or animal a botulinum neurotoxin from *Clostridium botulinum* toxin of type A, B, C, D, E, F, G or a mixture of two or more botulinum neurotoxins wherein the neurotoxin or mixture of neurotoxins is free of the complexing proteins which naturally form complexes with botulinum neurotoxins and wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes.

Goeschel et al teach a method of treating patients that have torticollis spasmodicus, facial dystonias, torsion dystonia and spasticity with injections of botulinum toxin A (pages 98-99 and Table 3, page 101). Goeschel et al teach that among the patients treated were non-responders (patients that did not show improvement nor muscle weakness or atrophy after at least two successive treatments of neurotoxin). Goeschel et al teach that neutralizing antibodies were found in the sera of all non-responders (patients that have developed neutralizing antibodies against botulinum toxin A) (pages 98-99). Goeschel et al teach that neutralizing antibodies were the cause of therapeutic failure (page 101). Goeschel et al teach that second generation botulinum neurotoxin preparations should be devoid of toxoid and should be purified from concomitant proteins, this will reduce the load of foreign substances that might lead to untoward reactions (page 102). Goeschel et al do not teach a botulinum neurotoxin or mixture of two or more botulinum neurotoxins wherein the neurotoxin or mixture of neurotoxins is free of the complexing proteins which naturally form complexes with botulinum neurotoxins.

Goeschel et al do not teach the use of a botulinum toxin other than botulinum toxin A.

Borodic et al teach compositions comprising botulinum toxin B as an alternative to botulinum toxin A (see the Title). Borodic et al teach that the repeated injections of botulinum toxin A leads to lack of effectiveness and sensitivity to botulinum toxin A (pages 182-183). Borodic et al teach that neutralizing antibodies to botulinum toxin A have been demonstrated using immunoassays (page 182). Borodic et al suggest that

because botulinum toxin B is immunologically distinct from botulinum toxin A it may have differing biologic effects at the cellular level and may also be useful as adjuvant therapy for patients resistant or refractory to botulinum A toxin (page 189).

It would be *prima facie* obvious at the time the invention was made to treat patients having cosmetic conditions, wherein the patient exhibits neutralizing antibodies against botulinum toxin A with botulinum toxin B because Borodic et al teach compositions comprising botulinum toxin B, which is immunologically distinct from botulinum toxin A and botulinum toxin B may have differing biologic effects at the cellular level and may also be useful as adjuvant therapy for patients resistant or refractory to botulinum A toxin. It would be expected barring evidence to the contrary, that botulinum toxin B preparation would be effective in treating cosmetic conditions because botulinum toxin B is immunologically distinct from A but has been demonstrated to have therapeutic effects similar to botulinum toxin A.

5. Claims 11-13 are rejected under 35 U.S.C. 103(a) as unpatentable over Goeschel et al, *(Experimental Neurology, 147, 1997, pages 96-102* in view of Shelley et al *(J Am Acad Dermatol. 1998, 28:227-9)* in view of Borodic et al *(Ophthalmic Plastic and Reconstructive Surgery, Vol 9, No. 3, p. 182-190).*

Claims 11-13 are drawn to method of treating a human or animal with a cosmetic condition treatable with a botulinum neurotoxin comprising administration to the human or animal a botulinum neurotoxin from *Clostridium botulinum* toxin of type A, B, C, D, E, F, G or a mixture of two or more botulinum neurotoxins wherein the neurotoxin or

mixture of neurotoxins is free of the complexing proteins which naturally form complexes with botulinum neurotoxins and wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes wherein the cosmetic condition is hyperhidrosis.

Goeschel et al teach a method of using botulinum toxin to treat patients having torticollis spasmodicus, facial dystonias, torsion dystonia and spasticity patients (pages 98-99 and Table 3, page 101). Goeschel et al also teach patients that have developed neutralizing antibodies against botulinum toxin A (pages 98-99 and Table 3, page 101). Goeschel et al teach that neutralizing antibodies were the cause of therapeutic failure (page 101). Goeschel et al teach that second generation botulinum neurotoxin preparations should be devoid of toxoid and should be purified from concomitant proteins, this will reduce the load of foreign substances that might lead to untoward reactions (page 102).

Goeschel et al do not teach the cosmetic condition, hyperhidrosis.

Shelley et al teach a method of treating patients that have hyperhidrosis with botulinum toxin A (page 228). Shelley et al teach that treatment with botulinum toxin A abolished hyperhidrosis one week after treatment (page 228). Shelley et al teach that BOTOX (botulinum toxin A) is a safe and effective treatment for hyperhidrosis (227).

Goeschel et al and Shelley et al do not teach a composition that comprises a botulinum toxin other than botulinum A.

Borodic et al teach compositions comprising botulinum toxin B as an alternative to botulinum toxin A (see the Title). Borodic et al teach that the repeated injections of

botulinum toxin A leads to lack of effectiveness and sensitivity to botulinum toxin A (pages 182-183). Borodic et al teach that neutralizing antibodies to botulinum toxin A have been demonstrated using immunoassays (page 182). Borodic et al suggest that because botulinum toxin B is immunologically distinct from botulinum toxin A it may have differing biologic effects at the cellular level and may also be useful as adjuvant therapy for patients resistant or refractory to botulinum A toxin (page 189).

It would be *prima facie* obvious at the time the invention was made to used the botulinum toxin B as taught by Borodic et al in the method of treating patients with hyperhidrosis that have developed neutralizing antibodies against botulinum toxin complexes of Goeschel et al and Shelley et al combined because Borodic et al teach that botulinum neurotoxin B can be used as an alternative to botulinum toxin A to treat cosmetic disorders (i.e. hemifacial spasm) and Shelley et al has demonstrated that botulinum toxin A is effective in treating cosmetic disorders (i.e. hyperhidrosis). It would be expected barring evidence to the contrary, that a botulinum toxin B preparation would be effective in treating patients with hyperhidrosis since Borodic et al teach that botulinum toxin B is immunologically distinct from botulinum toxin A and may be useful as adjuvant therapy for patients resistant or refractory to botulinum A toxin (page 189).

6. Claims 11-12 and 14-15 are rejected under 35 U.S.C. 103(a) as unpatentable over Keen et al *(Plastic and Reconstructive Surgery, July 1994, 94, No.1, pages 94-99)* and further in view of *(U.S. Patent No. 5,512,547 published April 30, 1996).*

Claims 11-12 and 14-15 are drawn to method of treating a human or animal with a cosmetic condition treatable with a botulinum neurotoxin comprising administration to the human or animal a botulinum neurotoxin from *Clostridium botulinum* toxin of type A, B, C, D, E, F, G or a mixture of two or more botulinum neurotoxins wherein the neurotoxin or mixture of neurotoxins is free of the complexing proteins which naturally form complexes with botulinum neurotoxins and wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes wherein the cosmetic condition is facial wrinkles.

Goeschel et al teach a method of using botulinum toxin to treat patients having torticollis spasmodicus, facial dystonias, torsion dystonia and spasticity patients (pages 98-99 and Table 3, page 101). Goeschel et al also teach patients that have developed neutralizing antibodies against botulinum toxin A (pages 98-99 and Table 3, page 101). Goeschel et al teach that neutralizing antibodies were the cause of therapeutic failure (page 101). Goeschel et al teach that second generation botulinum neurotoxin preparations should be devoid of toxoid and should be purified from concomitant proteins, this will reduce the load of foreign substances that might lead to untoward reactions (page 102).

Goeschel et al do not teach the cosmetic condition, facial wrinking.

Keen et al teach a method of treating patients that have hyperkinetic facial lines (wrinkles) with injections of botulinum toxin A (see the Abstract and pages 95-97). Keen et al teach that botulinum toxin A injections eliminated hyperfunctional facial lines (wrinkles) in healthy aesthetic surgical patients (page 94). Keen et al teach that antibodies to botulinum toxin A have been described in patients receiving much larger dosages of botulinum for long periods of time and the antibodies can render the toxin non-effective but do not harm the patient. Keen et al teach that the use of botulinum toxin A is a safe and efficacious method of nonsurgically eliminating facial wrinkles in aesthetic surgical patients for a period of 4 to 6 months (page 99).

Goeschel et al and Keen et al do not teach a composition comprising a botulinum neurotoxin other than botulinum toxin A.

Borodic et al teach compositions comprising botulinum toxin B as an alternative to botulinum toxin A (see the Title). Borodic et al teach that the repeated injections of botulinum toxin A leads to lack of effectiveness and sensitivity to botulinum toxin A (pages 182-183). Borodic et al teach that neutralizing antibodies to botulinum toxin A have been demonstrated using immunoassays (page 182). Borodic et al suggest that because botulinum toxin B is immunologically distinct from botulinum toxin A it may have differing biologic effects at the cellular level and may also be useful as adjuvant therapy for patients resistant or refractory to botulinum A toxin (page 189).

It would be *prima facie* obvious at the time the invention was made to used the botulinum toxin B as taught by Borodic et al in the method of treating patients with facial wrinkling that have developed neutralizing antibodies against botulinum toxin complexes

of Goeschel et al and Keen et al combined because Borodic et al teach that botulinum neurotoxin B can be used as an alternative to botulinum toxin A to treat cosmetic disorders (i.e. hemifacial spasm) and Keen et al has demonstrated that botulinum toxin A is effective in treating facial wrinkles. It would be expected barring evidence to the contrary, that a botulinum toxin B preparation would be effective in treating patients with facial wrinking since Borodic et al teach that botulinum toxin B is immunologically distinct from botulinum toxin A and is useful as adjuvant therapy for patients resistant or refractory to botulinum A toxin (page 189).

7. Claims 11-12 are rejected under 35 U.S.C. 103(a) as unpatentable over Goeschel et al, *(Experimental Neurology, 147, 1997, pages 96-102)* in view of Borodic et al *(Ophthalmic Plastic and Reconstructive Surgery, Vol 9, No. 3, p. 182-190)* and further in view of Jankovic et al *(The New England Journal of Medicine, April 25, 1991).*

Claims 11-12 are drawn to method of treating a human or animal with a cosmetic condition treatable with a botulinum neurotoxin comprising administration to the human or animal a botulinum neurotoxin from *Clostridium botulinum* toxin of type A, B, C, D, E, F, G or a mixture of two or more botulinum neurotoxins wherein the neurotoxin or mixture of neurotoxins is free of the complexing proteins which naturally form complexes with botulinum neurotoxins and wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes.

Goeschel et al teach a method of using botulinum toxin to treat patients having torticollis spasmodicus, facial dystonias, torsion dystonia and spasticity patients (pages

98-99 and Table 3, page 101). Goeschel et al also teach patients that have developed neutralizing antibodies against botulinum toxin A (pages 98-99 and Table 3, page 101). Goeschel et al teach that neutralizing antibodies were the cause of therapeutic failure (page 101). Goeschel et al teach that second generation botulinum neurotoxin preparations should be devoid of toxoid and should be purified from concomitant proteins, this will reduce the load of foreign substances that might lead to untoward reactions (page 102).

Goeschel et al do not teach a composition comprising a botulinum neurotoxin other than botulinum toxin A.

Borodic et al teach compositions comprising botulinum toxin B as an alternative to botulinum toxin A (see the Title). Borodic et al teach that the repeated injections of botulinum toxin A leads to lack of effectiveness and sensitivity to botulinum toxin A (pages 182-183). Borodic et al teach that neutralizing antibodies to botulinum toxin A have been demonstrated using immunoassays (page 182). Borodic et al suggest that because botulinum toxin B is immunologically distinct from botulinum toxin A it may have differing biologic effects at the cellular level and may also be useful as adjuvant therapy for patients resistant or refractory to botulinum A toxin (page 189).

The combination of Goeschel et al and Borodic et al as set forth above differs by not teaching the combination of more than 2 or all botulinum neurotoxins.

Jankovic et al teach the therapeutic uses of botulinum toxin (see entire article). Jankovic et al teach that botulinum toxin can be used to treat cosmetic conditions (i.e. hemifacial spasms)(page 1191). Jankovic et al teach that seven immunologically distinct

botulinum toxins have been identified (i.e. botulinum toxin serotypes A-G) (page 1188). Jankovic et al suggest that patients with antibodies against botulinum toxin will respond to injections with other botulinum toxins that are immunologically distinct from A.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to add any one of or all of the C, D, E, F or G botulinum toxins to the composition comprising "botulinum toxin B" neurotoxin combination of Goschel et al and Borodic et al as combined above because Jankovic et al that suggest that patients with antibodies against botulinum toxin will respond to injections with other botulinum toxins that are immunologically distinct from A and the addition of any or all of these neurotoxins would be readily expected to work given that botulinum toxin B has been individually shown to be effective for the treatment of cosmetic disorders.

Conclusion

8. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
June 27, 2004

PATRICIA A. DUFFY
PRIMARY EXAMINER